AMENDMENTS TO THE DRAWINGS

The attached sheet of drawings includes changes to Figure 1.

Attachment: Replacement sheet

REMARKS

Claims 1-16 are pending in the above-identified application. Support for the change to claim 1 is found at page 2, line 21 of the specification.

Unity of Invention Issues

Applicant respectfully maintains a traversal against the Unity of Invention Requirement for the same reasons indicated in the Response filed January 28, 2008. Applicant respectfully preserves the right to file a Divisional Application directed to the withdrawn claims 10, 12 and 16. In addition, it is respectfully requested that the Examiner consider withdrawn claim 12 for possible "re-joinder" if the present product claims are found to be allowable.

Specification Issues

The Office Action of May 23, 2008 included guidelines which illustrated the preferred layout for the specification. The specification has now been amended in view of these guidelines so as to include several sub-headings and a new section which briefly describes the drawing. Thus, it is requested that the objection to the disclosure of the present application be withdrawn.

Issues under 35 USC 103(a)

Claims 1-3, 7, 9 and 13 have been rejected under 35 USC 103(a) as being unpatentable over GlaxoSmithKline ("Prescribing Information; Navelbine (vinorelbine tartrate) Injection", 2002, Nov., pp. 1-17) and Duflos '377 (US 6,127,377).

Claims 1, 2, 4-7, 9 and 13 have been rejected under 35 USC 103(a) as being unpatentable over Wolgemuth '643 (CA 2,001,643) and Duflos '377.

Claims 8, 14 and 15 have been rejected under 35 USC 103(a) as being unpatentable over GlaxoSmithKline, Duflos '377, Wolgemuth '643, and further in view of Howell ("Anti-vascular effects of vinflunine...," *British Journal of Cancer* (2001) **84** (2), pp. 290-295.)

The above-noted rejections are traversed based on the following reasons.

Present Invention

The present invention is directed to a vinflunine pharmaceutical composition in the form of a stable and sterile aqueous solution of a water-soluble vinflunine salt at a pH between 3 and 4, which does not contain any sugar, sugar-based polyol or other preservatives, as recited in claim 1. As explained at pages 1-4 of the present specification, conventional pharmaceutical formulations containing vinflunine did not exhibit acceptable storage stability properties or required somewhat complex methods for preparing injectable formulations. However, the composition of the present invention overcomes these problems and exhibits advantageously improved storage stability properties without requiring complicated techniques or the presence of multiple preservatives. The improved stability properties exhibited by the composition of the present invention are evidenced by the test results described in connection with Examples 1 and 2 at pages 8-13 of the present specification.

Distinctions over Cited References

GlaxoSmithKline and Duflos '377 References

GlaxoSmithKline discloses a composition for intravenous administration which includes vinorelbine tartrate equivalent to 10 or 15 mg in water with no preservatives, wherein the aqueous solution is sterile and nonpyroginic. The pH of the composition is approximately 3.5.

Duflos '377 discloses vinca alkaloid antimitotic halogenated derivates of the vinblastine and viniorelbine family, including vinflunine as disclosed in the abstract thereof. Duflos '377 discloses vinflunine ditartrate at col. 13, lines 39-42.

Both GlaxoSmithKline and Duflos '377 fail to disclose or suggest the composition of the present invention containing a stable and sterile aqueous solution of a water-soluble vinflunine

salt at a pH between 3 and 4, which does not contain any sugar, sugar-based polyol or other preservatives. GlaxoSmithKline only relates to vinorelbine containing formulations. Duflos '377 mentions vinflunine, but fails to disclose any suggestion about formulating a vinflunine salt in an aqueous solution without preservatives as in the composition of the present invention. Duflos '377 also fails to suggest substituting vinflunine for vinorelbine in aqueous solutions with the expectation that similar stability properties would be exhibited.

It is alleged in the Office Action of May 23, 2008 that it would have been obvious for one skilled in the art to substitute the vinorelbine ditartrate described in GlaxoSmithKline with vinflunine ditartrate disclosed in Duflos '377 in order to arrive at the presently claimed invention. However, such a suggested substitution is not disclosed in GlaxoSmithKline or Duflos '377 and would not have been predictable in view of the significant differences in properties between vinorelbine and vinflunine. In fact, vinorelbine and vinflunine, even if they may have similar therapeutical properties, exhibit totally different physico-chemical properties in the form of a powder or in form of an aqueous solution. First, there are differences in water solubility: vinorelbine tartrate has a solubility higher than 1000 mg/ml whereas vinflunine tartrate has a solubility equal to only 290 mg/ml. Second, there are significantly different properties exhibited by each in the form of a powder after 6 months of storage at 5°C: vinorelbine tartrate degrades such that the major impurity is due to the oxidation of the alcohol group in the vindoline structure, whereas in contrast, vinflunine ditartrate degrades such that the major impurity is 23-0 dimethylvinflunine which is due to the hydrolysis of the ester group of the vindoline structure. Therefore, vinorelbine tartrate and vinflunine ditartrate generate very different major impurities. Third, the process for manufacturing vinflunine is totally different from the process for manufacturing vinorelbine. It is a more complex process since it requires a super acid medium. Fourth, vinorelbine exhibits fungicidal activity after up to 28 days of contact with mold spores, with a slight fungicidal activity after 24 hours of contact. In contrast, vinflunine exhibits no fungicidal activity. Consequently, several significant properties differ between these two compounds, such that one skilled in the art would not conclude it would be

predictable to employ one compound in place of another and expect the same physico-chemical properties to be exhibited together with any improved storage stability properties. Vinflunine seems to be less stable than vinorelbine since it has a lower solubility. Vinflunine degrades to form a major impurity significantly different from vinorelbine and does not exhibit fungicidal activity as does vinorelbine. Therefore, the behavior of vinflunine in an aqueous solution can not be predicted based on the different physico-chemical properties exhibited by vinorelbine.

Consequently, significant patentable distinctions exist between the present invention and both of the GlaxoSmithKline and Duflos '377 references, whether taken separately or hypothetically combined. Further, even if these references were hypothetically combined, there fails to be any recognition of the advantageously improved storage stability properties evidenced by the comparative experimental tests described in Examples 1 and 2 of the present specification which rebuts any allegation of *prima facie* obviousness based on this combination. Therefore, it is requested that the rejections based on these references be withdrawn.

Wolgemuth '643 Reference

Wolgemuth '643 is discussed at page 3, lines 26-32 of the present specification. Wolgemuth '643 relates to an injectable solution of vincristine, and discloses the use of an acetic acid/sodium acetate buffer to maintain a pH of the solution of between 3.5 and 5.5, preferably between 4.0 and 4.5. Wolgemuth '643 discloses at page 4, line 30 to page 5, line 3 that the described compositions may contain excipients, including sugars or polyols derived from sugars, such as mannitol. As described in Example 1 at pages 6-7 of the Wolgemuth '643, all the composition examples require mannitol. Although, Wolgemuth '643 may be interpreted to imply that the compositions therein do not require a sugar or sugar-based polyol, there fail to be any operative examples without such a component.

Wolgemuth '643 fails to disclose a composition which includes vinflunine. Wolgemuth '643 fails to disclose any examples which do not at least include a sugar-based polyol which is excluded from the composition of the present invention as recited in the present claims. Consequently, one skilled in the art would not find a disclosure or suggestion in Wolgemuth '643

to form compositions that do not at least contain a sugar-based polyol. Further, there fails to be any suggestion in Wolgemuth '643 to substitute vinflunine for vincristine. Consequently, significant patentable distinctions exist between the present invention and Wolgemuth '643 such that the rejections based on this reference should be withdrawn.

Howell et al. Reference

According to the Examiner, it would have been obvious in view of Howell et al. to increase the quantity of vinflunine as was been done for vinorelbine or vincristine in order to optimize the quantity and to obtain the claimed concentration claimed. First, it is submitted that Howell et al. fails to disclose or suggest the aqueous vinflunine composition of the present invention and fails to make up for any of the deficiencies noted above with regard to the other cited references. Secondly, as indicated above, vinflunine has a lower solubility than vinorelbine. Vinorelbine is used at a concentration of 10 mg/ml. As a consequence, it was not predictable that a stable aqueous solution of vinflunine having a concentration of between 25 and 30 mg/ml could be obtained, since an aqueous solution at 70 mg/ml precipitates after 2 months of storage at 5°C±3°C. Howell et al. fails to address this issue. Consequently, significant patentable distinctions exist between Howell et al. and the present invention, whether taken alone or hypothetically combined with the other cited references, such that the rejections based on this reference should be withdrawn.

It is submitted for the reasons above that the present claims define patentable subject matter such that this application should now be placed in condition for allowance.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____
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